Peer Review File
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Reviewer A

This is a report of a secondary analysis of a small uncontrolled trial of tumor treating fields added to standard of care. The authors note that patients with MGMT promoter methylation or TERT promoter mutation had longer progression-free and overall survival.

COMMENTS

1. This small single arm and thus uncontrolled trial was a priory unlikely to yield insight beyond showing the feasibility of adding TTF.

Reply 1: Thank you for your input. We will clarify in the text that this was exploratory data analysis outside of the initial primary endpoint of feasibility.
Changes in the text: "It should also be understood that this is an exploratory analysis of a phase I trial, and conclusions from this study were extracted outside of the initial endpoint of TTF feasibility."

2. There are a lot of misonceptions in the manuscript that must be fixed. For instance, in the title, the design of the analysis and of the trial precludes any statement on any "impact". To demonstrate impact on something, a randomized or at least controlled trial is necessary.

Reply 1: Point well taken.
Changes in the text: New title "Differences in clinical outcomes based on molecular markers in glioblastoma patients treated with concurrent tumor-treating Fields and chemoradiation: exploratory analysis of the SPARE Trial".

3. "Multiforme" does not exist anymore.

Reply 1: Thank you for highlighting. This was corrected and "multiforme" was removed from text.
Changes in the text: Multiforme removed from text.

4. The association of MGMT promoter methylation with outcome is known for 30 years.

Reply 1: Yes, this is true. Testing the survival benefit of MGMT was means to validate our other findings.
Changes in the text: N/A

5. The association of TERT promoter mutation with outcome reported here does not confirm several much larger clinical series such as Arita Acta Neuropathol Commun 2016; Nguyen Neuro Oncol 2017, Gramatzki EJC 2020.

Reply 1: Thank you for highlighting conflicting data from larger series. In this small study, we aimed to focus specifically on a patient cohort treated with TTF concurrently with radiation and

temozolomide.
Changes in the text: The discussion about conflicting data from previous studies has been expanded including the references that the reviewer added lines 252-261.

6. The comment on independence of TERT effects from IDH illustrates lack of understanding of the WHO classification. These alterations in their various combinations are now disease defining and not prognostic within entities. Further, there is only one trial showing benefit from TTF, not several ones (abstract) and at least the European guidelines do not consider TTF standard of care. The biases should be toned down.

Reply 1: The statement "even independent of IDH status was deleted". Reference 14 that followed that statement looked at prognostic significance of IDH and TERT mutations in a glioma cohort (pre updated WHO criteria). TERT promoter mutations are frequently present in IDH mutant 1p19q co-deleted oligodendrogliomas. Our analysis focused on IDHwt glioblastoma, however.
Changes in the text: Text was removed that mentioned "independent of IDH status". Abstract changed to "a large clinical trial". Abstract was edited to clearly state standard of care as per NCCN. A statement was added to clarify how TTF are not widely accepted: "Although it should be mentioned, TTF are still not widely accepted as standard of care for primary treatment of GBM internationally and not a part of the European Association of Neuro-Oncology treatment guidelines".

7. Finally, figure legend, survival is "better" by MGMT status, not "improved" (from where?)

Reply 1: Figure legend was corrected

Changes in the text: "Figure 1: 1A) Kaplan Meier survival curve showing better overall survival with methylated MGMT promoter. 1B) Kaplan Meier survival curve showing better overall survival with TERT promoter mutation"

Reviewer B

The manuscripts reads well and the major limitation of small sample size is mentioned. However, no proper discription of the used statistics is provided especially when stating that no molecular markers showed OS or PFS significance in single variable models - this issue should be corrected.
Reply: Thank you for your review. A statement was added in the methods and result sections to further elaborate on the Cox proportional hazard methods used for the statistical analysis.

Furthermore, the figure 1 missing in the pdf file.
minor spelling errors:
Line 50: with redundance
Line 109-110: font size needs adjustmend
Reply 1: Thank you
Changes in the text were applied